Screening for chlamydial infection in men: An evidence update

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ABSTRACT

Background
Chlamydial infection is the most common bacterial genital infection in the US with 1,244,180 cases documented in 2009. There are likely additional unreported cases because of presumptive treatment of disease, asymptomatic nature of genital infection, and lack of access to medical care. In 2007, the USPSTF published a recommendation statement to screen all sexually active nonpregnant women age 24 years or younger and older nonpregnant women at increased risk. Because of a lack of direct evidence on the effect of screening in men to reduce transmission to women, in reducing reinfection rates in men, or in preventing adverse health outcomes for men, they refrain from recommended for or against screening, leaving primary care clinicians and STD prevention programs with little guidance in practice.

Objectives
This systematic review was conducted to update the evidence for screening the sexually transmitted bacterial disease (STD), Chlamydia trachomatis in men, the screening effect on improving health outcomes, the evidence on the harms of screening and adverse events from treatment in men. This review will not assess existing recommendations that the USPSTF have already deemed “good” or “fair”.

Qualitative Methods
An analytic framework was developed by adapting the previously published work by the USPSTF on screening for Chlamydia infections in young women. From the framework, four key questions were developed to guide the literature search of articles published in PubMed-MEDLINE from 2000 through September 2010 and in the Cochrane Database of Systematic Review. Results were abstracted into tables, reviewed and assessed for methodological quality using criteria adapted from the STROBE statement.

Results
A total of 497 titles and abstracts were found from the initial search of databases plus 4 hand-selected articles from references of relevant articles. The final 8 articles that met all criteria were abstracted for data and rated for quality.
The search produced one “fair” but inconclusive study examining the effect of screening on disease frequency and no studies on changes in disease morbidity and mortality with screening. Two studies pertaining to positivity rates found significantly higher rates in men aged 19-24 and black Caribbean and unspecified black background. One fair and one good study found only mild to moderate harms from screening to conclude that benefits to screening were greater than the mild psychological harms. Lastly, one good meta-analysis concluded that doxycycline and azithromycin are equally efficacious in the treatment for Chlamydia in men and women with mild side effects including diarrhea, abdominal pain, and nausea.

Conclusions
There continues to be a lack of evidence on the effectiveness of lowering disease frequency, mortality and morbidity in women by screening asymptomatic men. Even while non-harmful screening tests and effective treatment of chlamydial infection are available, there is insufficient data to recommend any screening strategies of asymptomatic men at this time.
INTRODUCTION

Scope and Purpose

This systematic review was conducted to update the United States Preventive Services Task Force (USPSTF) review commissioned to search the evidence for screening the sexually transmitted bacterial disease (STD), Chlamydia trachomatis in 2001.\textsuperscript{1} In 2005, the USPSTF deemed an evidence update was necessary to strengthen weak recommendations and fill gaps in evidence, and in 2007 a focused review was published.\textsuperscript{2} Based on the two reviews conducted, the USPSTF concluded that good direct evidence existed to recommend non-pregnant females to receive screening for Chlamydia to reduce adverse health outcomes. However, due to the continued lack of evidence, the USPSTF was not able to make any new recommendation for screening men for chlamydial infection.

The focus of this review is to search for new evidence and synthesize the research with previously published review articles and update the recommendations for Chlamydia screening in men. This review will not assess the existing recommendations that the USPSTF have deemed “Good” or “Fair,” such as the evidence to screen non-pregnant or pregnant women. Likewise, this review will not cover the efficacy of infection treatment. Rather, this review will update the evidence on screening programs for men and its effect on improving health outcomes through improved prevalence and improved health outcomes for men and women in the population as well as examine evidence on the harms of screening and adverse events from treatment in men.

Prevalence and Burden of Suffering

Chlamydial infection is the most common bacterial genital infection in the United States.\textsuperscript{3} Since the Centers for Disease Control and Prevention (CDC) first surveyed the incident cases in
1941, Chlamydia has been documented as the most frequently reported STD in the US, nearly quadrupling the rate of syphilis, gonorrhea, and chancroid combined. Table 1 below shows the upward trend of reported disease in the U.S. However, interpretation of the rising incidence poses the epidemiological challenge of determining actual trends of disease prevalence in the community because increased screening seen in the last two decades leads to increased disease detection. However, the recent upward trend of Chlamydia is alarming; and even with recommended screening in women 25 and under, trends may indicate a persistent and high prevalence of chlamydial infection in the U.S population.

Figure 1. Chlamydia cases reported by state department: United States, 1984-2008*

Data from CDC, Sexually Transmitted Disease Surveillance, 2008.

The most recent surveillance report published in 2009 reported the highest number of cases ever documented at 1,244,180, and there are likely additional cases unreported or undiagnosed because of various factors, including presumptive treatment of disease, asymptomatic nature of genital infection, and lack of access to medical care. An estimated 2,291,000 individuals ages 14-39 were infected with C. trachomatis, based on the U.S. National
Health and Nutrition Examination Survey (NHANES).\textsuperscript{5} Prevalence estimates for adolescents and young adults have been found to be higher than that of the rest of the population. The U.S. NHANES survey estimated a 2.2\% (95\% confidence interval [CI] 1.8\%-2.8\%) prevalence for 14-39 year-old men and women, while the cross-sectional study of The National Longitudinal Study of Adolescent Health cohort of 18-26 year olds found an overall prevalence at 4.19\% (95\% CI, 3.48\%-4.90\%).\textsuperscript{6} The same study showed that Chlamydia was disproportionately prevalent in black women with the highest prevalence of 13.95\% (95\% CI, 11.25\%-17.18\%). In a review of published data from national sources including surveys of male adolescents, correctional facilities and data from the National Health and Nutrition Examination Survey (NHANES 1999-2002), the greatest burden of chlamydial infection is among men between ages 20 and 24 years.\textsuperscript{7} Chlamydial infections were disproportionately more prevalent in black and Hispanic men when compared to white men.

In addition to the health effects of genital infection, STDs are also a substantial economic burden on the U.S. healthcare system. The direct costs include clinic visits, diagnostic testing, treatment, treatment side effects, medication fees, and the treatment of possible complications from disease sequelae. In 2004, a review was published to estimate the direct costs of STDs in the U.S.\textsuperscript{8} Adjusted for the year 2000, the estimated the average cost per case for men was 20 dollars and for women 244 dollars. The total cost of chlamydial infection in the US was estimated at 250 million dollars per year, making Chlamydia the costliest bacterial STD, after the viral STDs HIV and genital herpes. Another study found that in women, 82\% of the cost per case is attributable to disease sequelae, whereas among men, 78\% of the estimated cost per case is attributable to acute infection.\textsuperscript{9} Another study found that indirect costs (wages lost from missed work, complications from treatment or missed treatment opportunities, hospitalizations,
etc) are as high as 540 million dollars per year.\textsuperscript{10} While cost analyses are often limited, these estimations underscore the substantial personal and economic burden of chlamydial infection and the necessity of effective preventive strategies to reduce the burden of this disease.

**Natural History**

Chlamydial infection is a sexually transmitted disease caused by the bacterium *Chlamydia trachomatis*. It causes genital infections in humans and can also manifest as trachoma and perinatal infections.\textsuperscript{11} In women, the bacteria proliferate and cause inflammation of cervical tissue, or mucopurolent cervicitis and ascend to the fallopian tubes, causing salpingitis and pelvic inflammatory disease (PID).\textsuperscript{12} Subsequent reinfection or prolonged untreated infection causes scar tissue to form around the inflamed tissue.\textsuperscript{13} Once symptomatic PID has occurred, there is a 1 in 6 chance a women will develop infertility.\textsuperscript{14,15} There is also risk of developing Bartholinitis and Fitz-Hugh-Curtis syndrome (perihepatitis).\textsuperscript{11} While in men symptoms and sequelae are less frequent, *C. trachomatis* can cause nongonococcal urethritis (NGU), proctitis, and epididymitis. Up to 42\% of NGU infections are asymptomatic, increasing the likelihood of transmission of the infection.\textsuperscript{16}

Human studies on the natural course of chlamydial infections are limited, but it is generally accepted that untreated infection can spontaneously clear over a period of months to years.\textsuperscript{17} However, reinfection does occur in women 20\% at one year, increasing the likelihood of complications.\textsuperscript{18,19,20} Another recent prospective study of women aged 14–17 found a reinfection rate as high as 31.3\% over three years.\textsuperscript{21}

**Risk Factors for Chlamydial Infection**

Sexually active individuals are at risk for acquiring chlamydial infection. While the infection can be acquired at any age, the highest rates occur in the late teens and early twenties.
Other risk factors include frequent changing of sexual partners, two or more sexual partners in a year, and a recent change in partner.\textsuperscript{22} According to surveillance data, the highest rates of chlamydial infection have been in the Southeast and West regions in the U.S. Also, higher incidence rates have been reported for women in all 50 states, almost three times the rate of men overall, which can most likely be attributed to the emphasis of screening programs directed towards women. The surveillance data also demonstrate increased chlamydial infection rates among blacks whose rates are eight times that of whites (1,519.3 cases per 100,000 in blacks compared to 173.6 in whites).\textsuperscript{3}

Less is known about the risk factors for chlamydial infection in men than in women. A Dutch study based on 21,000 men and women found chlamydial infection in men was associated with younger age, multiple sex partners, low education, low condom use, and complaints of frequent urination.\textsuperscript{23}

**Management of Infection**

**Treatment of Infected Person**

Two recommended regimens exist for the treatment of uncomplicated cases of chlamydial infection. A single oral dose of azithromycin (1 gram) or a seven-day course of doxycycline have been shown to be equivalent in both efficacy and tolerability and have shown a 92.1-97\% effectiveness in various studies.\textsuperscript{24,25,26,27} Longer courses of antibiotic regimens are required to treat complicated chlamydial infections such as PID and epididymitis.

**Treatment of Sex Partners**

Approximately 57-75\% of partners of infected individuals are infected with Chlamydia themselves.\textsuperscript{28,29} Partner notification programs have seen less than optimal results, likely due to the stigma associated with infection, differences in cultural beliefs between partners, and other
relationship dynamics.\textsuperscript{29} While out of the scope of this paper to provide guidelines for partner notification and treatment through patient or provider referrals, it is obvious that the evaluation and treatment of partners is an important component in controlling chlamydial infection in the population.

**Levels of Prevention and Screening**

Clinical practice should target various levels of strategies for STI prevention. The CDC recognizes three levels of prevention: primary, secondary, and tertiary STD prevention.\textsuperscript{30} Strategies for primary prevention of STI focus on prior to incidence or acquisition of disease and including public education, ad campaigns and billboards, and barrier methods such as condoms. Secondary prevention strategies aim to diagnose and treat an infected patient, such as universal screening of females for Chlamydia, and treatment with positive testing. Finally, tertiary prevention focuses on limiting complications and other negative health effects from disease such as treatment for PID and infertility.

There are a limited number of studies on primary prevention methods, especially in the high-risk youth population, but there are numerous studies on secondary and tertiary interventions for screening methods, treatment of STIs and management of their complications.\textsuperscript{31} Specifically, Chlamydia screening programs have been found to decrease disease burden and long-term health consequences, decreasing prevalence of complications like pelvic inflammatory disease by 60\%.\textsuperscript{32} Also, because the asymptomatic nature of chlamydial infection, screening, diagnosing, and treatment of unrecognized infection could prevent further transmission of disease. Further, screening tests are relatively rapid, affordable, and minimally invasive, especially if collected by urine. With these screening tools available for the detection of Chlamydia, it is important to continue to refine screening programs and to ensure that
appropriate high-risk populations are targeted to effectively reduce the disease burden in the population.

**Current Recommendations by the USPSTF**

In 2007, the USPSTF published a recommendation statement for screening for chlamydial infection. They recommend to screen for chlamydial infection in all sexually active nonpregnant young women age 24 years or younger and for older nonpregnant women who are at increased risk (A recommendation). Secondly, they recommend to screen for chlamydial infection in all pregnant women age 24 years or younger and in older pregnant women who are at increased risk (B recommendation).

The USPSTF recommend against routinely screening for chlamydial infection in women age 25 years or older, regardless of whether they are pregnant, if they are not at increased risk (C recommendation).

Lastly, they conclude that the evidence is insufficient to recommend for, or against routine screening of men due to the inability to assess the balance of benefits and harms of screening men (I statement). See Appendix A for USPSTF recommendation grading system.

**Current Practice**

Because most cases of chlamydial infections are asymptomatic, US Chlamydia control programs have focused on opportunistic screening of the higher risk age groups to diagnose and treat infection. Screening can be performed during routine physical exam visits, emergency room encounters, contraceptive counseling appointments, and primary care evaluations.

Current chlamydial infection screening rates are low, estimated at 41.6% among sexually active females aged 16-25 years according to a review of the Healthcare Effectiveness Data and Information Set (HEDIS) conducted by the CDC in 2007. The highest regional rate of
Chlamydial infection screening in 2007 was in the Northeast (45.5%) and the lowest was in the South (37.3%), with some states as low as 20%. The HEDIS is used by 90.0% of U.S. health plans to evaluate the quality of health-care services and benchmark performance and is a reliable data source for insured populations in the US. However, it is estimated that 18.4% of females aged 16–20 years and 28.2% aged 21–25 years were uninsured in 2007, meaning up to 4.8 million young women were less likely to access care and less likely to have resources to pay for chlamydial infection screening.35,36

Currently, it is recommended that all patients who have confirmed or suspected urethritis receive testing for gonorrhea and chlamydial infection because of the increased utility and availability of highly sensitive and specific testing methods and because a specific diagnosis might enhance partner notification and improve compliance with treatment, especially in the exposed partner.37 Treatment should be initiated as soon as possible after diagnosis.

Population-based cross-sectional studies have found high prevalence range of 6.8-10.1% in adolescent and young men.38,39 Even so, there are no recommendations for routine screening to detect infection in asymptomatic men for Chlamydia in the U.S.

**Chlamydial Screening Tests**

The previous USPSTF review found reliable and valid methods to screen and diagnose chlamydial infection in men.1 Culture analysis of urethral swab specimens is considered the diagnostic gold standard for chlamydial infection. However, acceptability of this mode of screening by patients and providers is restricted due to high expense, limited availability, a wait of 3 to 5 days for results, and the discomfort associated with invasive sampling.40

Nonculture antigen-detection tests (direct fluorescent antibody [DFA] assay and enzyme immunoassay [EIA]) and nonamplified nucleic acid hybridization based on DNA and RNA
technology are used in clinic as well, but still require invasive swabs for men to obtain specimens.¹

Tests using urine samples provide a more acceptable method of noninvasive specimen collection for both men and women. Accurate, reliable, and valid tests antigen-detection tests and DNA and RNA amplification tests are also available. A disadvantage of the amplification tests is that Chlamydia DNA can be detected up to 21 days after treatment because of the presence of nonviable organisms, possibly affecting test of cure or reinfection rates.⁴¹

**Rationale for Chlamydial Screening in Men**

A significant proportion of males and females infected with *C. trachomatis* are asymptomatic and do not seek testing or treatment. Unless they are screened, these individuals provide an ongoing reservoir for infection with the potential to transmit infection to partners and reinfect themselves. Without routine screening, most infections identified and treated among men are the result of symptomatic management or diagnostic testing⁴² or through referrals from provider or partner notification programs.⁴³ However, increasing rates of chlamydial infection and high rates of reinfection question the effectiveness of current screening practices to control and reduce the burden of disease. Testing only women is not sufficient to reduce the prevalence in high-risk populations. As men have a role in the transmission and reinfection of infection in women, screening men is a logical strategy to reduce the overall burden of disease.

**Controversies about Chlamydial Screening in Men**

Although screening for chlamydial infection among men can lead to increased treatment in women and can theoretically lead to reduced infection rates in women by reduced transmission, evidence that the burden of disease in women decreases when men are screened has been lacking. Instead the USPSTF reached different conclusions about chlamydial infection
screening in men, concluding that control programs should focus on improving the low rates of screening in women. The USPSTF concluded that there is a lack of direct evidence on the effect of screening and treatment in men to reduce transmission to women, in reducing reinfection rates in men, or in preventing adverse health outcomes for men. This lack of recommendation for or against screening has left primary care clinicians and STD prevention programs with little guidance to inform approaches to screening men for chlamydial infection.

Therefore, it is critical to fill evidence gaps by reinvestigating the literature. This paper will update the recommendations with new evidence on screening for chlamydial infection in men. Throughout this paper, the term Chlamydia will be used to mean C. trachomatis genital infection.
METHODS

This section of the review documents the literature search process used to develop and collect the evidence on screening men for the sexually transmitted infection, Chlamydia. Below we document the inclusion and exclusion criteria, Medical Subject Headings (MeSH terms) used, describe data abstraction methods, and how evidence tables were developed and analyzed. In all these steps, the author was the sole reader and abstractor of the evidence.

Analytic Framework

The analytic framework (Figure 2) was developed by adapting the previously published work by the USPSTF on screening for Chlamydia infections in young women. From the framework, four key questions (KQ) numbered below were developed to guide the literature search of gaps in evidence required to update the USPSTF recommendations.

Figure 2. Analytic Framework for Chlamydia Screening in Men
Critical Key Questions

<table>
<thead>
<tr>
<th>KQ1:</th>
<th>Does screening for Chlamydia in men reduce morbidity in men or women?</th>
</tr>
</thead>
<tbody>
<tr>
<td>KQ2a:</td>
<td>Does screening for chlamydial infection in men reduce the incidence of infection in men or women?</td>
</tr>
<tr>
<td>KQ2b:</td>
<td>Who should be screened? What are the risk factors for chlamydial infection in men?</td>
</tr>
<tr>
<td>KQ3:</td>
<td>What are the adverse effects of screening for Chlamydia in men?</td>
</tr>
<tr>
<td>KQ4:</td>
<td>What are the adverse effects of treatment for Chlamydia in men?</td>
</tr>
</tbody>
</table>

Key questions, which guided the literature review, were identified as areas with unresolved issues since the previous USPSTF recommendations. Questions not included in this review are accuracy of screening instruments used or the efficacy of treatment in men as previous reviews have found sufficient evidence to support available satisfactory diagnostic instruments and treatment for Chlamydia. The sections below details the methods used for the literature search process.

Literature Search Strategy

An initial search was performed using PubMed-MEDLINE for systematic reviews (SR) and meta-analyses (MA) published from 2000 through September, 2010 and in the Cochrane Database of Systematic Review (CDSR) in September 2010 on screening for Chlamydia in men. Searches for articles specific to each KQ were conducted to supplement evidence found in the initial search. SRs and MAs were reviewed at the abstract stage and the articles were reviewed for relevance to each key question and graded for quality.

This review will focus on the evidence of the effectiveness of screening strategies in men, as well as evidence that screening and treating Chlamydia in men improves health outcomes in
both men and women. This review will also focus on the adverse effects of screening, as previous reviews found gaps in the evidence, limiting the ability of the Task Force to make recommendations for or against screening. Inconvenience, social stigma of sexually transmitted diseases, partnership discord and exacerbation of domestic violence among partners, and concern related to testing errors were among the adverse effects explored in the literature. In this report, screening is defined as testing performed on asymptomatic persons. Universal screening means that everyone is tested, regardless of symptoms or risk factors. Selective screening tests only individuals who meet specific criteria.

**Key Question 1 and 2**

After the initial search of SR and MA conducted, a literature search was performed for controlled trials of Chlamydia screening from 2000 through September 2010 in PubMed-MEDLINE and the Cochrane Central Registry of Controlled Trials (CCRCT). The Medical Subject Heading (MeSH terms) *Chlamydia* was combined with the terms *screening* and *men*. All search terms are listed in Appendix C. In KQ 2, all abstracts found for KQ1 were reviewed for data on changes in disease frequency in the population.

**Key Question 3**

In addition to the initial search for SRs and Mas, all abstracts located for KQ1 and KQ2 were reviewed for screening-associated harms. An additional search on PubMed-MEDLINE was conducted from 2000 through September, 2010 to locate large observational studies addressing adverse effects by searching for publications that included terms to capture harms generally (adverse events, harms) and potential harms suggested earlier in the review (inconvenience, social stigma, etc.) without restrictions related to study design.
Key Question 4

In addition to the initial search for SRs and Mas, all abstracts located for KQ1, KQ2, and KQ3 were reviewed for treatment-associated harms. An additional search of PubMed-MEDLINE from 2000 through September, 2010 was performed to locate large observational studies addressing adverse effects by searching for publications that included medication terms or discontinuation of medication without restrictions related to study design.

Inclusion/Exclusion Criteria

A set of inclusion and exclusion criteria was developed and applied generally, with specific additional criteria applied as needed to answer each key question. See Appendix D for list of specific inclusion and exclusion criteria used for each KQ.

Populations and Disorders

The population of interest of this review includes sexually active men in the US, Canada, UK, Australia, New Zealand as well as other western European countries when data were not adequate for a specific key question. While this review specifically focuses on Chlamydia, studies with other STDs were included if outcomes of diseases were measured separately. Studies with a primary focus on other sexually transmitted infections such as AIDS, syphilis, and gonococcal infections were not included. Studies including only Chlamydia positive men (reinfected) or HIV positive men were also excluded as this review focuses on general screening programs for asymptomatic men in the population. Studies of both men and women were also included if measured outcomes for screening men were found separately.

Settings

Primary care, emergency room, school based locations, STD clinic or other community practices and settings were included in this review.
Screening

Studies about screening programs were included if they provided descriptions of the study population, including number of men screened, age range, setting, and other important socioeconomic factors. Screening program features such as time course of the study, type of testing, and type of test were also abstracted into evidence tables. Studies were included if they use a recommended screening test, and screening trials must have used the screening results in the care of the intervention participants.

Risk Factors

Studies of risk factors for Chlamydia were included if they reported the number of men screened, age, setting, reason for visit, and other socioeconomic factors. Screening criteria used, type of Chlamydia test, and prevalence rate of the tested population were abstracted into evidence tables.

Treatments

Studies that used the first line agents azithromycin and doxycycline were included if they were used in the treatment of Chlamydia such as from a positive test or urethritis. Because we wanted to include all harms associated with treatment of Chlamydia, second line medications were included as well (tetracyclines, erythromycin, etc.). However, treatment of complications such as epididymitis and proctitis were excluded.

Outcomes

Outcomes of interest were changes in frequency of infection in the women or the total population. Health outcomes of interest included: treatment of Chlamydia, changes in frequency of related sequelae, reinfection rates, quality of life ratings, change in sexual behavior practices, or change in health status. KQ3 and KQ4 focused on harms associated with screening or
treatment including inconvenience, social stigma of sexually transmitted diseases, possible discord and exacerbation of domestic violence among sexual partners, and concern related to testing errors, serious medical events and discontinuation.

Quality

“Good” and “fair” quality papers are included in this review. Summaries of all papers, including “poor” quality studies can be found in the abstractions tables (Appendix G). See section below for discussion of methodology of data abstraction and quality assessment.

Date and Language

Only articles published in English between 2000 and September 2010 were included in literature search.

Data Abstraction and Quality Assessment

Only results pertaining to screening men were abstracted into tables, as programs that screen women only are out of scope with this paper. All resulting studies were reviewed and assessed for methodological quality. Adapted from the STROBE statement for reporting observational studies, a standardized abstraction form was used to critically appraise the quality of studies in regards to the following possible categories: (1) completeness of study description of intervention and comparison populations; (2) sampling method and potential for selection bias; (3) completeness of study intervention description; (4) validity and reliability of the measurement of exposure; (5) validity and reliability of the measurement outcome; (6) appropriate statistical analysis; (7) attrition, loss to follow-up; and (8) identification and discussion of potential biases and confounding, with or without analysis adjustments to control.44,45 The STROBE statement does not specify criteria for assessing quality of the study.
For the purposes of this review, quality of studies was determined by the number of limitations: good (0-2 limitations), fair (3-4 limitations), or poor (5-8) quality.

**Literature Synthesis**

Because of the diverse methodologies among reviewed studies, a qualitative synthesis of the literature is detailed in this review paper. A quantitative synthesis was not conducted, although data from published meta-analyses for KQ4 on the adverse effects of treatment was included. For each Key Question, the results of the literature review are critically synthesized using papers of “good” and “fair” quality.
RESULTS

Literature Review Process

A total of 497 titles and abstracts were found from the initial search of databases and 4 hand-selected articles from references of relevant articles (See Appendix E for search results and flow chart). After 165 duplicate articles or studies were removed, and remaining articles were sorted by titles and abstracts for relevance. The full-text versions of the remaining 63 articles were skimmed for inclusion and exclusion criteria of the applicable key question(s). The final 8 articles that met all inclusion and exclusion criteria were then abstracted using the created table and rated for quality as detailed in the methodology section. Below are the results for each key question.

Key Question 1: Does screening for Chlamydia in men reduce morbidity in men or women?

The literature search did not produce any new study published which used biological outcomes of morbidity or mortality of women and men when screening men for Chlamydia in the designated time period.

Key Question 2a: Does screening for Chlamydia in men reduce the incidence of infection in men or women?

Summary of findings

The literature search produced one “fair” quality study that followed a screening program for male inmates and the effects of test positivity in women from the surrounding areas. Men incarcerated in the Philadelphia prison system have received systematic screening examinations for Chlamydia since 2002. Using ZIP codes of the prisoners to identify areas of “high-treatment” versus “low-treatment,” investigators were able to compare changes in test positivity of
neighborhood women during the two years before the start of the screening program and the three years after.

Researchers found that both high-treatment and low-treatment areas had a decline in test positivity. In high-treatment areas, positivity significantly declined from 10.6% in 1999, 8.7% in 2001 (p<0.05). In low-treatment areas, positivity decreased as well; 7.3% in 1999, 5.5 in 2001, and 4.2 in 2004 (p<0.05). While these results are statistically significant decline in test positivity, the downward trend started even before the prison screening program was implemented. With numerous limitations in bias and confounding variables, investigators were not able to conclude that the decline in the rate of positivity in women was due to the prison screening program.

Study Details (Appendix G, Table 1)

Peterman 2009

In a retrospective comparative study using data from the Philadelphia STD control program and Region III of the Infertility Prevention Project (IPP), investigators analyzed the influences of a male screening program on the rate of test positivity of women over a 5-year period to document rates 2 years before implementation of the program and 3 years after. They collected test results from women 20 to 24 years-old, who tested in family planning clinics operated by IPP. This age group was selected because several other testing sites are available to women in Philadelphia, specifically high-school programs that are meant to target 15 to 19 year-old women. Investigators have therefore excluded younger-aged women from the analysis to eliminate this confounding variable, which may give the appearance of a declining prevalence in the community.

Test results from the family planning clinics were categorized by geographic area using ZIP codes of residences for men treated for Chlamydia and released from prison. By using the
2000 Census for population estimates of 20 to 24 year old men in each ZIP code, investigators designated the highest 18 areas with a proportion of prisoners receiving treatment to compare with the lowest 18 areas of treatment. In 2002 to 2004, 4263 positive Chlamydia tests were reported in Philadelphia for men aged 20 to 24, of which 34.7% of were diagnosed in the prison system. During that period, 1,054 prisoners of the high-treatment ZIP codes were identified, treated and released from jail. The high-treatment area had a populations of 23,203 men aged 20 to 24, and a treatment rate of 1.5% each year. In low-treatment areas, 98 prisoners were treated in a population of 21,057, or 0.12% annually.

Researchers found that test positivity for women in the high-treatment areas decline over time from 10.6% in 1999, to 8.7% in 2001, and 7.4% in 2004 (p<0.05). The relative rate of annual decrease was greater even before implementation of the male prisoner screening program. Similarly, test positivity for women in the low-treatment areas declined over time from 7.3% in 1999, to 5.4% in 2001, and 4.2% in 2004 (p<0.05).

**Key Question 2b: Who should be screened, and what are the risk factors for Chlamydia?**

**Summary of findings**

The literature search resulted in four studies pertaining to risk factors and associations with Chlamydia testing positivity. The literature search produced one of “good” quality, one “fair” quality, and two “poor” quality studies that identified possible risk factors for Chlamydia positivity which could be used to improve effective detection of infection in men.

A “good” quality study of a comprehensive Chlamydia screening program in the UK included 97,121 men with an overall Chlamydia positivity rate of 7.6%. They found that men aged 19 to 24 experienced a rapid increase in risk as compared with 16 year-old adolescent men. Positivity was also higher in black men than white men, and when reporting a new partner in the
last 3 months, or having two or more partners in the last year. This study found there was slightly higher detection of Chlamydia in family planning centers, and lower positivity rates in hospitals. Otherwise, positivity rates were only slightly variable depending on screening setting.

In a “fair” quality study conducted in the U.S., investigators looked at positivity rates in adolescent men tested at school-based health centers. Using a self-administered questionnaire on sexual behaviors, data was collected to compare demographic characteristics and sexual health behaviors associated with Chlamydia positivity. The results show an overall prevalence of 6.8% positivity in 1,434 middle-school and high-school aged students from Baltimore and Denver. In the Denver cohort, condom use with their main (OR 0.30, 95% CI, 0.10, 0.91) or casual partner (OR 0.15, 95% CI, 0.03, 0.78) was protective against infection. In Baltimore, age was the only statistically significant risk associated with infection (OR 1.47, 95% CI, 1.23, 1.75). In multivariate analysis of several variable, age greater than 16 (AOR 1.34, 95% CI, 1.11, 1.62) and black race (AOR 2.37, 95% CI, 1.21, 4.63) were associated with testing positive. While there are limitations of self-reported data, under-reporting of negative sexual behaviors and over-reporting of condom use, suggest that there may be associations may be stronger than the results reflect.

Study Details (Appendix G, Table 2)

Simms 2009

The Health Protection Agency of the United Kingdom implemented the National Chlamydia Screening Program (NCSP) in 2003, which seeks to offer annual screening for all sexually active men and women under age 25. In 2007, with full participation of local primary care commissioners in England, this study was conducted to examine the variations of Chlamydia positivity throughout the country.
For each of the 334,902 screening tests performed, of which 29% were men, multiple variables were collected, including gender, age, race, recent sexual partner history, and Chlamydia test result. They found and overall Chlamydia positivity of 7.6% in men. Using 16 year old white males screened in general practice, multivariate analysis showed rapid increase in positivity with ages 19 [AOR: 2.58 (95% CI, 2.25, 2.94)] to 24 [AOR: 2.84 (95% CI, 2.49, 3.24)]. Risk of positivity was higher among young men of black Caribbean [AOR: 2.02 (95% CI, 1.79, 2.27) and black background unspecified [AOR: 1.90 (95% CI, 1.61, 2.24)]. When compared with patients screened in the general practitioner’s office, only screening test done at community contraception services and youth clinics had statistically significant higher positivity rates. Multivariate analysis showed that for men, risk of positivity increased significantly with age (P < 0.0001), ethnicity (P < 0.0001), clinic setting (P < 0.0001), a new sexual partner in the past 3 months (P < 0.0001), and reporting 2 or more sexual partners in the year (P < 0.0001).

*Joffe 2008*[^39]

In order to improve cost-effectiveness of Chlamydia programs targeted for men, a group of investigators studied risk and protective factors for asymptomatic men in schools or school-based health centers (SBHC) in the Baltimore and Denver areas. From 1999 through 2003, they recruited high school and middle school children. In Baltimore, all men were enrolled with parental approval for complete well-adolescent examinations and were asked to complete the Guidelines for Adolescent Preventive Services (GAPS) questionnaire, which was developed by the Department of Adolescent Health of the American Medical Association[^48]. The questionnaire covers a broad array of health behaviors topics, including sexual health. If the student indicated they were sexually active, a first-catch voided urine specimen was collected for Chlamydia and Gonorrhea testing. Sexually active men were also given a second questionnaire, the Baltimore
Region III chlamydia data form that included questions about symptoms, recent sexual activity, and condom use. Patients seeking care at the SBHCs for urogenital symptoms were excluded from the study. Recruitment methodology was different in Denver, in that men were not recruited during a wellness exam, but during acute care visits and sports physicals.

In Baltimore, 56% (n=1090) students accepted screening; in Denver, 17% (344) men accepted screening, for a total of 1,434 enrollees. Prevalence for chlamydia was 7.5% and 4.7% in Baltimore and Denver, respectively, with an overall prevalence rate of 6.8%. Their study showed that in the Baltimore cohort, age greater than 16 was associated with an increased risk of chlamydia positivity [OR 1.47 (95% CI, 1.23, 1.75)]. In the Denver cohort, self-reported condom use with either the last main [OR 0.30 (95% CI, 0.10, 0.91)] or casual partner [OR 0.15 (95% CI, 0.03, 0.78)] had protective associations. In multivariate analyses of both cities that included age, race, history of STI, sexual partner history and condom use, only age at 16 and older [AOR 1.34 (95% CI, 1.11, 1.62)] and black race [AOR 2.37 (95% CI, 1.21, 4.63)] were associated with testing positive for chlamydia. No other variables were statistically significantly associated with chlamydia positivity.

Key Question 3: What are the adverse effects of screening for Chlamydia in men?

Summary of findings

In weighing evidence for and against screening, known and potential harms must be considered. The most frequently discussed adverse effects of screening for Chlamydia are the psychological, emotional, and social impacts of receiving testing and receiving a positive diagnosis. Known harms of screening include anxiety, both about the test and about potential results, stigmatization, fear of partner’s reaction, and fear of future fertility from a positive diagnosis. The literature search produced two good-to-fair studies examining the adverse effects
of screening men and women. One study conducted in the United Kingdom surveyed 842 individuals aged 16-35 years old for anxiety, depression and self-esteem at three points in time: before screening, at screening, and after receiving a negative result. Though not statistically significantly different, the study found that women had generally higher levels of anxiety, depression, and lower self-esteem. Particularly, men’s anxiety levels decreased after screening, whereas women were only relieved after a negative result. Another cross-sectional study conducted in Denmark found that among 277 participants who received the screening test, 25.6% (n=71) were unaware that they could have Chlamydia and received screening test after being offered by the general practitioner. Of the 71 participants, 11.3% (n=8) felt stigmatized by being offered testing, while 82% (n=58) felt satisfied. Among infected individuals, 34% of sexual partners were upset by the diagnosis and 10% of relationships ended.

Study Details (Appendix G, Table 3)

Campbell 2006

In the 2006 article describing the ClaSS project, 842 individuals were randomly selected from a pool of 19,773 men and women registered in the National Health Service in the Bristol and Birmingham areas of the UK for an invitation for home-based screening for Chlamydia and for answering questionnaires to assess levels of anxiety, depression, and self-esteem at three time points: before the invitation for screening, at screening, and after a negative result. Using a fixed proportion randomization scheme, individuals were randomly selected to receive an invitation letter from their general practitioner followed by the study packet including information on how to provide home-collected urine sample and/or vulval swab sample. Initially designed as a prospective cohort study, the low response rates from the first four practices compelled investigators to select independent cross-sectional randomized samples of individual at each of
the three time points, stratified by sex and practice, as well as limiting the age bracket to 16-26 year old. The main outcomes were assessed by using the Hospital Anxiety and Depression Scale (HADS), a simple and reliable questionnaire and valid when used in community settings and primary care medical practice. The Rosendburg Self-Esteem Scale was also used to measure stigmatizing effects of screening for Chlamydia. In the analysis, the cohort and cross-sectional groups were combined after assessing similar response rates, similar outcomes after adjusting for age and sex.

The investigators found that in general men reported experiencing less negative impacts of screening than women when considering all three time periods. While there was not statistically significant differences between genders, mean scores were 6.52 (SD = 3.60) and 6.27 (SD = 3.38) for 16-25 year old and 26-39 year old men, respectively. Women had mean anxiety scores of 8.14 (SD = 3.89) and 8.28 (SD = 3.63) for the same age groups. Depression scores were lower in younger age groups, and lowest in men aged 16-25. Mean depression scores were 3.01 (SD = 2.8) and 4.12 (SD = 3.6) for 16-25 year old and 26-39 year old men, respectively. Women had mean depression scores of 3.63 (SD = 3.2) and 4.42 (SD = 3.2) for the same age groups. Self-esteem was similar for age groups and sex, but was slightly lower in young women.

The investigators also investigated changes in anxiety, depression, and self-esteem levels across time. They found statistically significant (p=0.0049) decreases in mean anxiety levels before, during (-0.66, 95% CI -1.23,-0.09), and after screening (-0.99, 95% CI -1.60,-0.38) and evidence that the pattern was different for men and women (p=0.012 for interaction). Men anxiety levels occurred after submitting their test sample, and women anxiety levels only decreased after receiving a negative result. There was no increase in anxiety as a result of receiving the invitation; however, this only captures individuals who responded to the
questionnaires. There was not a clear pattern of depression and self-esteem across the three time points. While depression was lower and self-esteem was higher after receiving a negative test results, findings are not significant and no clear interpretations can be concluded.

While there were no significant differences between men and women overall, the results of this study show that large population-based screening for Chlamydia does not have deleterious impact on the psychological well-being of those tested. Having an invitation for screening and during screening did cause increases in anxiety and depression and decreases in self-esteem, but these were not lasting with relief with a negative result. In fact, sub-analyses showed that men were less negatively affected by screening, and psychological improvements were seen immediately after submitting testing samples.

*Kangas 2006*  

A cross-sectional survey of 277 men and women was conducted in Denmark to quantify potential psychosocial effects of testing for Chlamydia and receiving a positive or negative diagnosis. In Aarhus County, where the study was performed, 90% of Chlamydia tests are performed in general practices. Investigators recruited 91% of all the general practices in the county. Patients coming for a visit were recruited by their general practitioners by being asked if they would be screened for Chlamydia and mailed the survey within a week.

The survey addresses three topics that were found to be areas of concern from the few studies on the psychological impacts of screening of women participants: the magnitude of stigmatization, partner’s reaction to positive diagnosis, and anxiety over future reproductive health. Participants were divided into two cohorts for analysis of outcome: the proportion of those with a positive diagnosis was compared with those with a negative diagnosis, and sub-analysis was also performed for gender.
A total of 277 (81.2%) individuals’ mailed responses were included in the study with 64 individuals failing to respond after a reminder letter. Among these participants, 28 individuals were Chlamydia-infected men and 73 were non-infected men (n=101). When asked stigmatization of having a positive diagnosis, 50% of infected men and 56% of non-infected men felt it was a private matter and would not tell anyone (p=0.549). 46% of infected men and 18% of non-infected men felt they would be embarrassed to talk about testing with others. Concerning questions directed to their reaction to receiving test results, 14% of infected men were upset, 21% felt despair, 29% felt embarrassed, and 32% felt no emotional impact. In contrast, non-infected men were not upset (0%; p=0.007), 4% felt despair (p=0.022), 3 felt embarrassed (p<0.001), and 34% felt no emotional impact (p=0.708). On topics concerning psychosocial impacts in relation to their sexual partner among those with a positive diagnosis, 25% felt “dirty”, 43% felt relieved, and 75% of partners were understanding. Among those with a negative diagnosis, none felt “dirty” (p<0.001), 10% felt relieved (p=0.450), and equally 75% of partners were understanding (p=0.891). 83 of the 101 men tested had requested Chlamydia testing because of suspected exposure, exposed partner, previous infection, new partner, or others. The remaining 18 men were offered testing by the GP. Of these 18 men, 16 (88.9%) was satisfied with the offer, 1 (5.6%) felt stigmatized, and 1 (5.6%) felt no emotional impact.

Key Question 4. What are the adverse effects of treatment for Chlamydia in men?

Summary of findings

The literature search resulted in one good meta-analysis that reported overall efficacy rates and adverse effects of medication including discontinuation as the measures of impact of adverse effects associated with antibacterial treatment of genital Chlamydia.52,53
Adverse effects associated with treatment for Chlamydia included tolerability of medication—typically diarrhea, abdominal pain, nausea, vomiting, dyspepsia, and constipation. Other adverse events examined were evidence of serious and rare medical events associated with the most common antibacterial agents doxycycline and azithromycin as well as less commonly prescribed antibacterial medications.

**Study Details (Appendix G, Table 4)**

*Lau 2002* 54

A meta-analysis of twelve randomized clinical trials evaluated the efficacy and tolerance of azithromycin and doxycycline for genital Chlamydia in 1542 patients for microbial cure of infection and 2171 patients for adverse events. The review searched multiple databases from 1975 to 2001 for randomized controlled trials of oral doxycycline and azithromycin in males aged >15 and nonpregnant females aged >15 with evaluation of microbial cure with CT biological assay negativity at a 2-5 week follow-up.

In the azithromycin group, microbial cure occurred in 853 of 884 patients (96.5%) and in the doxycycline group, 645 of 659 (97.9). Adverse events were reported by 319 of 1274 (25.0%) azithromycin-treated patient and 205 of the 897 (22.9%) of the doxycycline-treated patients. The pooled efficacy difference between the two antimicrobial agents is 0.008 (95% CI, -0.007-0.022, p=0.296) and was not statistically significant. The pooled risk difference was also not statistically different at 0.009 (95% CI, -0.19-0.037, p=0.533).

The most frequently reported adverse events were gastrointestinal in nature (87.3%) including diarrhea, abdominal pain, nausea, vomiting, dyspepsia, constipation, flatulence, and other unspecified symptoms. Other non-gastrointestinal symptoms included fatigue, malaise, sweating, dizziness, headache, skin rash, fever, and other unspecified symptoms. There were no
studies that looked at a study population of only men with Chlamydia. However, we can assume that biologically, men and non-pregnant women would have similar adverse effects—mostly typically mild GI symptoms. There were no major adverse events documented in the review, and both regimens of azithromycin and doxycycline were found to be equally safe and efficacious.

There were some limitations on the quality of the review (limitations = 4, “fair quality”) that prevent broad generalization to the safety profile of azithromycin and doxycycline. The review does not discuss the characteristics or demographics of the populations studied in each of the trials. However, it is unlikely that differences in socioeconomic status and different provider care settings should affect biological harms of the antibiotic treatment received. Also, the review does not assess the method of recording adverse events used in the different studies. It is possible that come methodologies are less reliable than others, such as self-reported events versus a thorough interview by a health care provider or anonymous questionnaire.
DISCUSSION

Screening men: Effects on Chlamydia burden in men and women

Despite efforts to decrease the burden of Chlamydia infection in women through national recommendations, the impact of screening programs for women alone has not been clear. Confounded by increased detection with increased screening, incidence of Chlamydia continues to rise with increased risk for reproductive complications. Screening of asymptomatic men is a strategic approach to detect, treat, and prevent the transmission of the STI. However, there is a paucity of studies that look at the effects of this disease control method on the changes in frequency in the population and no studies on changes in disease morbidity and mortality.

The literature produced only one study, which was of “fair” quality, with inconclusive findings. By focusing on a small subsection of the prison-based screening in Philadelphia and its effects on women aged 20 to 24 seen in family planning clinics, there is a high degree of internal validity as well as generalizability to the broader population of Philadelphia and the rest of the U.S. Furthermore, there were issues in methodology and using ZIP codes to designate overlapping sexual networks between the prisoners and neighborhood women. Also, 20 to 24 year old men may have been engaging in sexual relationships with younger-aged women who were excluded from the study. With too many unknown variables confounding the relationship between male screening and changes in positivity rates in women, the findings from this study are inconclusive. Screening men for Chlamydia remains difficult because asymptomatic men seek health care infrequently. Prison-based screening programs are a good potential to detect and treat latent infections, however the impact on disease prevalence is difficult to determine. The lack in research and well-conducted studies that investigate the relationship between screening
men with biological outcomes in women preclude any determinations on the effectiveness of this disease prevention method.

**Risk Factor Identification**

Infected but asymptomatic young men are an elusive group to screen for STIs because they are not likely to seek medical care when feeling well, unlike their female counterparts who tend to have more regular visits for general reproductive health. Therefore, descriptive studies can guide screening programs for men in order to enhance cost-effectiveness, and efficiency in capturing positive cases.

The English study on the NCSP dataset was based on one of the most comprehensive Chlamydia screening programs performed in the UK and was of “good” quality. However, coverage of the target population was low (4.9%), and as a result, may not represent all young men at risk of Chlamydia infection. Because population prevalence could not be ascertained, positivity was appropriately used as the outcome measure, with 16 year-old white men as the referent group. The study found that positivity was significantly higher for men aged 19-24 and black Caribbean and unspecified black background. These findings indicate that screening programs must ensure that services are available not only to school-aged children, but target young adults as well. The high positivity rates may indicate high prevalence of Chlamydia in this study population. As only 29% of screening tests in the study were men, new strategies to increase participation must be implemented to ensure all men at risk receive equitable and accessible health services.

Joffe et al. conducted a “fair” quality study that looked at male students in the Baltimore and Denver areas. There were a few areas of concern in the methodology and analysis of the study. Because the two study populations of Baltimore and Denver were so different in
demographics, analysis was performed both separately and together. This may have weakened the power of the study, as the number of participants in Denver was low. Additionally, the study does not specify the conditions under which the questionnaires were administered. It is unlikely that responses remained anonymous, as it was also used as a tool by providers to discuss health concerns. This is concerning for the reliability of the responses used to analyze risk factors for Chlamydia. The self-reporting nature of their healthy behaviors may not accurately reflect true behavior. Students may be embarrassed and under-report poor sexual health habits and over-report safe sexual practices. Because of this bias, associated risk and protective factors may be more strongly associated with STI positivity than the study reports. The overall positivity rate of 6.8% among only asymptomatic men in this study indicate that SBHCs can be an appropriate health care setting, especially in high-prevalence areas, to identify and treat chlamydia infection in asymptomatic men. SBHCs can provide STI screening and counseling on sexual behavior at the start of sexual activity that is accessible without transportation, available at convenient hours, and at affordable costs. More school-based studies and analyses are needed to guide future screening recommendation for adolescent aged children.

**Adverse Effects of Screening**

There is a paucity of studies that investigate the harms of screening men for chlamydia in large population-based screening programs. The literature review produced two cross-sectional survey studies of good and fair quality assessing the psychological impacts of screening both men and women that included analyses of men alone.

The ClaSS study from the UK had moderate issues with selection bias and study design, but can still be considered a “good” study. There is a moderate degree of selection bias of volunteering participants and results may reflect a population with less psychological morbidity.
It is quite possible that the non-responders have a different psychological profile, but this is difficult to assess. Also, data on post-result levels of psychological distress, the survey only captures individuals with negative results. We can assume that anxiety, depression and low-self-esteem will continue in those that have a positive result, but these patients will likely follow-up with their GPs, receive appropriate therapy and behavior counseling to reduce future risk of STI acquisition.

The ClaSS study found that women experience anxiety, depression, and self-esteem more intensely than men, but not with statistical significant. However, the ClaSS project did find that and increases in anxiety and depression and lower self-esteem experienced with an invitation for screening by the general practitioner decreases once the patient has undergone testing. This is different than women who experience continued distress until receiving a negative result. When screening for sexually transmitted infections there is always the potential for increasing psychological morbidity regardless of whether there are overall health benefits of screening. This study has policy implications to include men in screening for Chlamydia as part of large screening programs, as they do not seem to have serious injuries to their psychological health.

As for the Danish study by Kangas, screening practices for Chlamydia are different in Denmark from that of the US. There are four clinical instances for individuals to receive testing: (1) patients are experiencing symptoms; (2) asymptomatic people with frequent sex partner change; (3) women under 26 before intrauterine device insertion or hysterosalpingogram; and (4) as part of the small opportunistic screening program. There is however no national screening program in place in Denmark. Rather only two communities receive annual chlamydia testing through pilot programs using register-based postal invitations. Also, the questionnaire used in the study was based on previously published qualitative studies on British women. Men and
women may think differently about these issues, as may the Danish and US population in general as well. However, this survey addresses the psychological stresses and anxieties of testing and can be applied to a broad population of sexually active youth.

Considering the limitations of this article (4), this “fair” study of both Chlamydia-positive and negative men have similar reactions to Chlamydia testing. However, men felt some degree of embarrassment and stigmatization, most men were satisfied with testing, and the majority of men felt to emotional impact from test answer, and felt relief.

The findings from both these studies are consistent with similar small-scale surveys observed for other screening program, which suggest that individuals are unlikely to suffer profound or long-lasting emotional effects as a result of participating, and that the experience may even have a positive effect on their well-being. For example, a recent questionnaire-based survey of a random sample of men and women aged 15 to 29 who responded to an invitation for be screened for chlamydia by means of a home based urine sample in the Netherlands, found that 42% felt relief at receiving a negative result and that only a small minority of those receiving a negative result remained anxious.56 Also, men react differently than women, generally being less influenced by having a test offer and a positive or negative test result. Therefore, it is feasible to incorporate men in universal screening programs in a preventive strategy. However, conditions of anxiety, stigma, and depression, even if temporary, are important topics that require appropriate counseling by health care providers for both men and women.

**Adverse Effects of Treatment**

There was no randomized study found that directly compared the intensity and duration of adverse events associated with azithromycin and doxycycline. The single “fair” meta-analysis by Lau, et al. concludes that the efficacy of doxycycline and azithromycin were equal and safe
for the treatment of Chlamydia in men and women. Approximately 23-25% of patients report adverse events with each antibiotic, mostly gastrointestinal in nature including complaints such as diarrhea, abdominal pain, and nausea.

For the purposes of assessing harms with treatment for Chlamydia, the investigators assumed that adverse events in males treated for chlamydial urethritis are comparable to those in males treated with the identical regimen for nongonococcal urethritis of any etiology. Given that urethritis is a local infection and the pharmacokinetics is unlikely to vary with different infectious etiologies of urethritis, this is a reasonable assumption. This allowed investigators to capture more data and possible rare negative events. Even so, both antibiotic regimens were found to be equally safe and efficacious.

Under these controlled trials, estimates of therapy efficacy can be overestimations under close observation and optimal conditions. In actual practice, efficacy may be compromised by partial compliance, especially for doxycycline, which is a longer multi-dose regimen. The compliance of the patient and length of therapy must be considered when selecting an appropriate therapy for Chlamydia. Patients may be more likely to take azithromycin as prescribed as a one-time dose, versus doxycycline which is indicated twice a day for seven days and result in treatment failure. A physician might conclude that azithromycin is the treatment of choice. The cost differential between single-dose and multi-dose therapy makes the medication choice a central issue in the environment of limited resources, and a comprehensive cost-effectiveness analysis should be performed and dose–response trials may also be needed to evaluate less complicated doxycycline regimens, which can increase its safety profile and its affordability.
CONCLUSION

Like previous systematic reviews published on chlamydia screening in men, there continues to be a lack of evidence on the effectiveness at lowering disease mortality and morbidity in women.\textsuperscript{1, 2} Obviously, there is a need for more research and studies of well-conducted randomized trials establishing a direct relationship between screening men and control of disease burden through decreased prevalence of Chlamydia cases, PID, and other related complications. Chlamydia infection is both a very treatable and preventable infectious disease, yet it persists in the population, particularly in the young and black populations, leading to unnecessary health risks and complications. To complement recommended screening of young women, screening asymptomatic men is a logical strategy for the treatment of latent infections and to prevent transmission, reinfection between partners, and the development of complications. However, there is insufficient data available to recommend any screening strategies of asymptomatic men at this time.

The studies reviewed in this paper reveal that the harms of screening and treatment are mainly mild psychological distress associated with testing. However, the relief of receiving confirmation of negative test or treatment for a latent infection exceeds the harms. Likewise, treatment for Chlamydia is affordable and accessible, safe and effective. Further, it is important that any screening program is part of a larger control effort which includes education, counseling safe sexual behaviors, and promoting condom use.

The high prevalence of Chlamydia in asymptomatic men suggests a role for a broad screening program. Future research must incorporate current knowledge of risk factors for a screening strategy that is efficient at capturing men who infrequently seek out medical care, and effective in actually reducing the burden of disease.
APPENDIX

Appendix A. USPSTF Recommendations Grading Classification*†

<table>
<thead>
<tr>
<th>Grade</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strongly recommends that clinicians provide [the service] to eligible patients. The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.</td>
</tr>
<tr>
<td>B</td>
<td>Recommends that clinicians provide [this service] to eligible patients. The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF makes no recommendation for or against routine provision of [the service]. The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against routinely providing [the service] to asymptomatic patients. The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.</td>
</tr>
<tr>
<td>I</td>
<td>The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.</td>
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</table>

†The USPSTF grades reflect the strength of evidence and magnitude of net benefit.

Appendix B. Summary of Evidence Reviewed on Screening Men for Chlamydial Infection

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<thead>
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<th>Variable</th>
<th>Grade</th>
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<td>Evidence that screening reduces morbidity and mortality in men</td>
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<tr>
<td>Evidence that screening reduces disease frequency in men and women</td>
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<tr>
<td>Evidence of identifiable risk factors to create targeted screening programs for men</td>
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<tr>
<td>Harms of screening</td>
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<tr>
<td>Harms of treatment</td>
<td>Fair</td>
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Appendix C. Search Strategies

Table 1. Systematic Review on PubMed-MEDLINE

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<tr>
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<td></td>
</tr>
<tr>
<td>3 screen*</td>
<td></td>
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<td></td>
</tr>
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<td>5 #1 OR #4</td>
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<td>7 #5 AND #6</td>
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Table 2. Systematic Review on Cochrane Database of Systematic Reviews

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<td>2 screen*</td>
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<tr>
<td>3 Men OR male</td>
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Table 3. Screening Trials

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</tr>
<tr>
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</tr>
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<td>2 (Men OR male)</td>
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</tr>
<tr>
<td>3 screen*[TIAB] / screen*:ti,ab (Cochrane)</td>
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### Table 4. Screening Harms

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</tr>
<tr>
<td>2. Screen*</td>
</tr>
<tr>
<td>3. Case finding</td>
</tr>
<tr>
<td>4. casefinding</td>
</tr>
<tr>
<td>5. #2 OR #3 OR #4</td>
</tr>
<tr>
<td>6. #1 AND #5</td>
</tr>
<tr>
<td>7. Men OR male</td>
</tr>
<tr>
<td>8. #6 AND #7</td>
</tr>
<tr>
<td>9. Adverse*</td>
</tr>
<tr>
<td>10. Harm*</td>
</tr>
<tr>
<td>11. Label*</td>
</tr>
<tr>
<td>12. Stigma*</td>
</tr>
<tr>
<td>13. Violen*</td>
</tr>
<tr>
<td>14. #9 OR #10 OR #11 OR #12 OR #13</td>
</tr>
<tr>
<td>15. #8 AND #14</td>
</tr>
</tbody>
</table>

### Table 5. Treatment Harms

<table>
<thead>
<tr>
<th>Observational Studies of Treatment Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Database:</strong> PubMed-MEDLINE, Cochrane Database</td>
</tr>
<tr>
<td><strong>Limits:</strong> Dates: 2000 October 2010, English language</td>
</tr>
<tr>
<td>1. Chlamydia*</td>
</tr>
<tr>
<td>2. Treatment</td>
</tr>
<tr>
<td>3. Antibact* OR antibiotic*</td>
</tr>
<tr>
<td>4. (#1 AND #2) OR (#1 AND #3)</td>
</tr>
<tr>
<td>5. Men OR male</td>
</tr>
<tr>
<td>6. #4 AND #5</td>
</tr>
<tr>
<td>7. Advers*</td>
</tr>
<tr>
<td>8. Harm*</td>
</tr>
<tr>
<td>9. Discontinu*</td>
</tr>
<tr>
<td>10. #7 OR #8 OR #9</td>
</tr>
<tr>
<td>11. #6 AND #10</td>
</tr>
</tbody>
</table>
Appendix D. Inclusion and Exclusion Criteria for Key Questions

Key Question 1 and 2: Screening Trials and Morbidity or Prevalence

Inclusion Criteria
1. Screening: study of Chlamydia screening in men; outcomes same as listed above.

Exclusion Criteria
1. Does not meet quality criteria.
2. None of the outcomes listed above.
3. Focus on women or pregnancy-related screening.
4. Does not meet any inclusion criterion.
5. Not a general primary care population.
6. Not English language or non-developed country.
7. Non-comparative study/excluded design.
9. Screen not used in clinical care.
10. Pure modeling study.

Key Question 3: Screening Harms

Inclusion Criteria
1. Study addressing adverse events associated with Chlamydia screening in men.

Exclusion Criteria
1. Does not meet quality criteria.
2. Focus on pregnancy-related screening.
3. Does not meet any inclusion criterion.
4. Not generalizable to primary care population
5. Not English language or non-developed country

Key Question 4: Treatment Harms

Inclusion Criteria
1. Systematic review, large cohort, or large prospective observational study addressing adverse events associated with Chlamydia treatment or screening in men.

Exclusion Criteria
1. Focus on inpatient, prison, MSM community, or other high risk group
2. Focus on interventions other than antibiotics.
3. Does not meet quality criteria
4. None of the adverse effects of interest to our review above.
5. Focus on pregnancy-related screening.
6. Does not meet any inclusion criterion.
7. Not a general primary care population
8. Not English language or non-developed country
9. Not a study design specified above.
Appendix E. Standardized Abstraction Table

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Design</td>
<td>RCT, descriptive studies, etc.</td>
</tr>
<tr>
<td>Source and study Population*</td>
<td>N. Age, sex, race/ethnicity, SES, and other description of demographics. Eligibility criteria? How were they recruited? Well described?</td>
</tr>
<tr>
<td>Missing data*</td>
<td>Drop outs, adherence, crossovers, attrition, loss to follow-up. Alternative analysis?</td>
</tr>
<tr>
<td>Intervention*</td>
<td>Diagnostic test? Time period? Well described?</td>
</tr>
<tr>
<td>Measurement of exposure*</td>
<td>Potential confounding? Reliable and valid measurement instruments? Training or blinding? Reliable, valid, and equal? Time period?</td>
</tr>
<tr>
<td>Measurement of outcome*</td>
<td>Potential confounding? Reliable and valid measurement instruments? Training or blinding? Reliable, valid, and equal? Time period?</td>
</tr>
<tr>
<td>Analysis*</td>
<td>Intent to treat? Power analysis, control for design effects? Appropriate data analysis?</td>
</tr>
<tr>
<td>Results</td>
<td>Primary outcome measurement with confidence intervals, statistical significance</td>
</tr>
<tr>
<td>Bias and Confounding*</td>
<td>Possible confounding and biases identified and discussed? Any adjustments?</td>
</tr>
<tr>
<td>Limitations</td>
<td>Summary and score 0-8</td>
</tr>
<tr>
<td>Overall quality</td>
<td>Good = 0-2, Fair = 3-4, Poor 5-8</td>
</tr>
</tbody>
</table>

*Categories used to assess study quality and limitations for grading
Appendix F. Search results and article flow

497 Found from search
4 Hand selected
501 articles

165 duplicate articles or studies

336 articles reviewed by title

186 removed for irrelevance by title

150 articles reviewed by abstract

87 removed for irrelevance by abstract

63 articles read

51 excluded based on criteria

8 articles abstracted and assessed for quality

2 excluded based on poor quality

6 studies included in review
### Appendix G. Evidence Tables

#### Table 1. Summary of articles on screening for Chlamydia in men to reduce incidence in men or women (Key Question 2a)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peterman et al. 2009</td>
<td>Question: Does a screening program targeting men influence test positivity of CT infection in women from neighboring areas? Design: Retrospective study cross-sectional comparison</td>
<td>Philadelphia population is about 1.5 million in 2000. Investigators wanted to study the effects of CT testing and treatment of men on the prevalence of women in the same geographic area of Philadelphia. Investigators divided city into areas based on percent of men diagnosed and treated for CT via the prison screening program.</td>
<td>Women 20 to 24 years old receiving CT testing at 56 family planning clinic sites in Philadelphia. 70,309 tests in the area reported for a population of 62,657 women. 5664 (8.1%) cases of CT reported. No other demographic information given.</td>
<td>Loss to attrition and follow-up does not apply to this study. ZIP codes were largely undocumented for CT negative inmates. Therefore, it is difficult to assess any geographic distribution or high-prevalence and low-prevalence areas. This was excluded from the study. Instead investigators compared high-treatment and low-treatment areas.</td>
<td>First, this study has excluded younger women from the study to adjust for testing in other centers. However, most CT infection in women are in younger ages, so any effect will be smaller in the 20 to 24 age group. Second, because this intervention of male screening was performed in prison, it is difficult to assess the relationship they have with 20 to 24 year old women being seen in family planning clinics. Philadelphia prison/jail chlamydia screening program. Average of 30,000 prisoners released yearly from Philadelphia prison system from 1996 to 2003. 86% are men 30% are 18 to 24 years old 70% black 20% white 10% Hispanic. Most common reason for incarceration is “pre-trial hold” (n=19,098 in 2003) for a median of 17 days. 91% of identified CT among 20 to 24 year olds was successfully treated with single dose of Azithromycin (1g) or 7 day course of doxycycline (100mg twice a day).</td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Summary of articles on screening for Chlamydia in men to reduce incidence in men or women (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Measurement of exposure/outcome</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
<th>Results</th>
<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peterman et al. 2009</td>
<td>Change in test positivity for CT among 20 to 24 year old women</td>
<td>Philadelphia receives federal funding from IPP for CT testing. Since 1995, policy was to screen all women &lt;30 who attend family planning clinics and all women &lt;35 who attend STD clinics. Starting in 1997, all CT testing was done using NAAT technology Geographic areas were defined using ZIP codes for men testing positive in prison. The 2000 census was used to estimate the number of men and women living in ZIP codes, which was then used to estimate the proportion of men treated for CT in prison for each ZIP code. A total of 47 ZIP codes were ranked for proportion of CT treated in prison. The 18 highest treated areas were compared with the 18 lowest. The middle 11 were excluded as it was used to develop analytic approach.</td>
<td>Women testing at family clinic sites are only a small proportion of women at risk for CT infection. With a small sample, shifts in family practice year-to-year can cause significant changes in rate positivity. For example, testing can also performed in juvenile detention facilities, adult prisons, public school, and family court. The article has attempted to adjust for these other screening programs and have excluded women 15-19 who may be receiving CT testing in school. Also, impossible to assume partnerships with women of community and men released from prison. We know 34.7% of all CT infections in men from 2002 to 2004 were diagnosed in the prison system; women may be getting infected from other sources.</td>
<td>15 to 19 year old women were excluded from the analysis to address possible confounding in findings of prevalence. Because 16-19 year old can be tested in other sites like schools and not family planning clinics, results may give appearance of a false decline in community prevalence.</td>
<td>70,281 tests in Philadelphia prison among all men: 16,860 in 2002 27,721 in 2003 25,700 in 2004</td>
<td>4263 total positive cases among 20 to 24 year old men in 3 years 1479 (34.7%) were diagnosed in prison</td>
</tr>
<tr>
<td>CT=C.trachomatis</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 2. Summary of articles for risk factors associated with Chlamydia positivity (Key Question 2b)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simms, I et al. 2000</td>
<td>Question: What are the positivity rates of Chlamydia by different variables? Design: Retrospective prevalence study of national database</td>
<td>Men and women under 25 who live in England (5.3 million people) Program criteria: Opportunistic testing for sexually active under 25 Asymptomatic, without genital symptoms</td>
<td>370,012 total screening tests  • 11,564 excluded for missing gender or test result  • 23,546 ineligible age (&gt;25) 334,902 tests available for analysis  • 29% men</td>
<td>Data was excluded if gender data was missing.</td>
<td>NCSP is a national program managed at the local level. Per NCSP protocol, tests are offered at every opportunity, including routine medical follow-ups and other acute care visit Depending on location, various practices may more aggressively offer CT testing, causing regional differences in CT testing and positivity. Also, acceptance rates are low, especially for men. Some potential for confounding, and is difficult to ascertain prevalence of population.</td>
<td>NAAT testing for CT in urine For each screening test, 12 variables were collected, which included geographic location, demographics, sexual partner history, and test results. Sexual history is taken, and patients are advised of full STI screen, and safe sexual practices are advised.</td>
</tr>
</tbody>
</table>

NCSP=National Chlamydia Screening Programme, NAAT=nucleic acid amplification test, CT = C.trachomatis (cont.)
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Measurement of exposure/outcome</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
<th>Results</th>
<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simms, I et al. 2000</td>
<td>Laboratories are certified under standard NCSP protocol. Per NCSP protocol, staffs are trained regularly and refreshed by local commissioners.</td>
<td>Some concern for self-selection, as this is voluntary program. Those with higher perceived risks will more likely seek care. Also, there are varying patterns of testing by location. Some health settings screen more aggressively than others, and could result in lower positivity rates. Also, because of infectious nature of CT, can have higher prevalence areas that can confound risk factors for positivity. Because of large, nationalized scale of study, bias and confounding are only a moderate concern.</td>
<td>Variables included for analysis: age, gender, ethnicity, new sex partner in last 3 mo, &gt;2 partners in 1 yr. Variation in positivity by location was explored using funnel plots. Means calculated and 2-sided standard errors used to distinguish statistically significant variables. Univariate and multivariate logistic regression used to explore risk associations (OR) Men and women were analyzed separately.</td>
<td>Overall positivity in men was 7.6% Age: 16 as referent group. AOR (95% CI)</td>
<td>1: Measurement of exposure: While there is strict protocol for offering testing eliciting sexual history, there was wide variation between geographic locations and types of health clinics. However, there was appropriate analysis using funnel plot to identify outlying areas. Location was among the adjusted variables in multivariate analysis.</td>
<td>Good</td>
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</tbody>
</table>

NCSP=National Chlamydia Screening Programme, CT=C.trachomatis, OR=odds ratio, AOR=adjusted odds ratio, CI=confidence interval, * p<0.05
|-------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------|----------------|---------------------------------------------------------------------------------|---------------------------------|
| Joffee, A et al. 2008   | Question: What are the risk factors for Chlamydia in school-aged children to increase benefit and cost-effectiveness of screening programs? | Number of sexually active (eligible) students was not measured due to infeasibility. Eligibility criteria: any man attending high school or middle school with a SBHC Enrolled Oct 1999-Jan 2003 | 1434 men attending a SCHC in high school or middle school  
- 344 males from Denver (from 6 middle and 8 high schools)  
- 1090 males from Baltimore (7 high school-only SBHCs)  
11-21 years in age  
Two study arms are not comparable—Baltimore has an older group, recruiting only high-school aged males, being seen as part of a wellness examination  
In Denver, both middle school and high schools were included. Men were recruited during acute care visits and other visits, not including urogenital infections (ie sports physicals)  
Men were excluded from the study if they indicated symptoms of STD infections at time of screening, those who specifically sought STI services, or those who were referred by disease intervention specialist. | No discussion of missing data. | Moderate. Participation requires enrollment in school with SBHC and parental consent. Students are more likely to be educated with parents concerned in their health. Self-selected participation for screening. Especially in Denver, acceptance rates are low, but they were recruiting during acute cases (respiratory illness, sports injuries, etc.) | In Baltimore, males completed the Guidelines for Adolescent Preventive Services (GAPS) questionnaire. For a general healthy behaviors, including sexual behaviors including:  
- Current symptoms, number of sexual partners, new partners, condom use, etc.  
If sexually active, were asked to provide first-catch voided urine specimen for CT and NG testing | SBHC=school based health clinic, CT=C.trachomatis, NG=N.gonorrhea |

Participants were given GAPS questionnaire which covers health behaviors, including sexual behaviors.  
Additionally, a second questionnaire, the Baltimore Region III chlamydia data form was administered in Baltimore, which covers current symptoms, recent sexual activity, number of sexual partners, and condom use with main and casual sex partners.  
There may be error in measurement due to self-reporting nature of questionnaire format. Participants may be less likely to report unhealthy behaviors, biasing towards null.  
Patients provide 20mL of first-catch clean urine for CT and NG testing by NAATs, both LCR and PCR were used with no statistically significant difference in sensitivities and specificity.  
Urine was processed and tested at approved and certified laboratories at local sites. Results were entered into database, and results sent to clinic for follow-up if required |
Table 2. Summary of articles for risk factors associated with Chlamydia positivity (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
<th>Results</th>
<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joffee, A et al. 2008</td>
<td>Before implementation of study, SBHCs did not offer urine based-screening for CT to asymptomatic men because of lack of funds. Relatively new strategy, so may have increase in errors.</td>
<td>Analysis was performed with SAS 9.1 Descriptive statistics and prevalence were conducted for all men together and separately for Baltimore and Denver cohorts. OR and 95% CIs were calculated for all men and separately for location. Univariate and multivariate analyses were performed for demographics and behavioral variables between men testing positively and negatively for CT Variables significant to 0.10 level in univariate analysis was entered in multivariate analysis Risk factor analysis was conducted for all men and separately for location to account for significant variables between the men from two cities</td>
<td>Screening acceptance rate: • 56% in Baltimore • 17% in Denver CT prevalence: • 7.5% in Baltimore • 4.7% in Denver • 6.8% overall Risk Factors [OR (95% CI)]: <strong>Baltimore</strong> Age &gt;16: 1.47 (1.23, 1.75)* Black race: 1.46 (0.58, 3.70) Prior STI: 1.49 (0.57, 3.88) Sex partner in 2 mo: 1.56 (0.86, 2.85) &gt;1 sex partner in 1 yr: 1.39 (0.85, 2.28) Condom with main partner: 0.76 (0.42, 1.35) Condom with casual partner: 0.79 (0.36, 1.73) <strong>Denver</strong> Age &gt;16: 1.37 (0.94, 2.0) Black race: 1.39 (0.49, 3.92) Prior STI: 3.01 (0.62, 14.5) Sex partner in 2 mo: 1.17 (0.33, 4.23) &gt;1 sex partner in 1 yr: 2.03 (0.69, 5.98) Condom with main partner: 0.30 (0.10, 0.91)* Condom with casual partner: 0.15 (0.03, 0.78)* <strong>Combined Adjusted OR</strong> Age &gt;16: 1.34 (1.11, 1.62)* Black Race: 2.37 (1.21, 4.63)*</td>
<td>Sampling and selection bias. With any targeted program, there is some loss of capturing all infections in community. While this program does identify young men with CT, it is still in the scope of school based health centers and still requires parental consent. Further, only 17% of students in Denver accepted study participation. Along with los sample size and low power, there is additional confounding factors that warrants more research to increase participation in future screening programs. Measurement of exposure: Some questions in training, as the protocol is newly implemented. Also, no mention of blinding or anonymity for participant privacy. Potential confounding and bias towards null. May underestimate protective and risk factors</td>
<td>Fair</td>
</tr>
</tbody>
</table>

SBHC=school based health clinic, CT=C.trachomatis, NG=N.gonorrhea, NAAT=nucleic acid amplification testing, OR=odds ratio, CI=confidence interval, * p<0.05
Table 2. Summary of articles for risk factors associated with Chlamydia positivity (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Hiltunen-Back et al. 2001 | Question: Are there identifiable patient profiles of chlamydia positive individuals to improve preventive strategies? | Multicenter study in Finland 12 STD clinics and non-STD clinics comprising the Sentinel STD Surveillance Network: 5 STD clinics, 2 university student health clinics, 3 general practices, and 2 gynecological clinics | 50,976 patients received screening in Sentinel STD Network Clinics in Finland from 1995-1997. • 32,230 patients were tested for Chlamydia in STD clinics • 18,746 patients were tested for Chlamydia in non-STD clinics | 97% acceptance of questionnaire reflects high participation. Loss to follow-up or attrition rates does not apply. However, does not mention missing data | No appointment and no payment necessary for clinic visits. Must be university student to utilize student clinic. Referral and payment is necessary to be seen at women’s clinic – due to high potential for selection bias, data from women’s clinic is excluded from study analysis. | Self-administered anonymous questionnaire with 21 points Questionnaire includes demographic data (age, gender, occupation, nationality, place of residence), reason for visit, symptoms, and screening by patient’s, partner’s, or physician’s suggestion. Questionnaire also included time and place of exposure, course partner if known and notified, and history of sexual partners, and participation of other risky sexual behaviors A physician performed physical. Samples for CT, GC, Syphilis, and HIV were routinely taken. Urine sample was cultured (1995) in McCoy cells or immunoassays and PCR/LCR (after 1995). | CT=C.trachomatis, GC=N.gonorrhea

(cont.)
Table 2. Summary of articles for risk factors associated with Chlamydia positivity (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Measurement of exposure/outcome</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
<th>Results</th>
<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiltunen-Back et al. 2001</td>
<td>All patients receiving care at STD clinics received questionnaire. 97% agreed</td>
<td>Fairly broad locations, free appointments and care. Again, some concern for external validity.</td>
<td>Patient data from STD and non-STD clinics were compared and those testing positive and those testing negative for Chlamydia. Analyses were performed for data collected over entire 3 year period. Initial subgroup analysis comparing 1995 and 1997 year showed same risk factor result. Variables with normal distributions were described with means and standard deviations. Statistical comparisons for groups were performed by t-test, z test, and analysis of variance. Ordinal variable were described with median and interquartile range and were compared using Mann-Whitney test of Kruskal-Wallis test. Measures with discrete variables were expressed as percentages and analyze by chi-square test.</td>
<td>3,686 had a positive Chlamydia test. 8.4% overall positivity rate 8.8% in men, 7.8% in women Age (mean, 95%CI) CT positive: 26.6 (25.9-27.3) CT negative: 31.7 (31.3-32.0) Prevalence in age group: 15 to 19: 14.3% 20 to 24: 13.6% 25 to 29: 10.8% Infection source partner: Casual partner: 60.9%, 95% CI 58.4, 63.4 Regular partner: 36.8%, 95% CI 34.4-39.2</td>
<td>5: Sampling/Source and study population Reliable internal validity of study. However, some questions with external validity remain. While a Western European nation with continuously high rates of CT, health system and social system of Finland is different from that of USA. It is likely a more homogenous group with access to free healthcare. Results reported from this study however are still valid and provide insights on key strategies for Chlamydia prevention. Additionally, unclear of recruitment and screening protocol of non-STD clinics. Measurement bias/Confounding/Analysis Because only CT positive patients received the questionnaire at the non-STD clinics, Chlamydia negative patients are only pooled from STD clinics. Two groups were not compared, and analysis did not account for this confounding variable.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

CT=C.trachomatis
Table 2. Summary of articles for risk factors associated with Chlamydia positivity (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rietmeijer et al 2008</td>
<td>Question: What are chlamydia positivity rates among males screened in various venues in the US? Design: Systematic literature review</td>
<td>PubMed Central and US National Library of Medicine’s online archives, 1995-2007 Search terms “male,” “chlamydia,” “screening,” “prevalence,” and “positivity” Additional manual search</td>
<td>Limited to asymptomatic men in clinical and nonclinical sites, excluding STD clinic settings 54 articles included for review. Studies collected in US</td>
<td>Due to variability in study type, test setting, testing methodologies, recruitment strategies, and reported subpopulations, meta-analysis was not possible in meaningful analysis. Because STD testing is standard of care in STD clinics and in symptomatic men, these populations were appropriately excluded for screening study. Through various recruitment strategies among studies, urine samples from male patients were screened for CT using NAAT.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Summary of articles for risk factors associated with Chlamydia positivity (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Measurement of exposure/outcome</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
<th>Results</th>
<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rietmeijer et al 2008</td>
<td>Abstracted data: overall male positivity rates, and if available, rates for race/ethnicity, age group, venue, and US region. Articles abstracted using tabular format conducted by one author, then independently verified and corrected if needed by main author</td>
<td>The main investigator is employed at the Denver Public Health Department. There are no details for funding source or other publication bias. It is not clear from article alone if a standardized method was used to assess study quality and internal validity.</td>
<td>Each category of abstracted data was tabulated to find: Median chlamydia positivity rate Interquartile range Number of observations Limitations and heterogeneity of data appropriately precludes meta-analysis and formal synthesis.</td>
<td>Overall median Chlamydia positivity rates ranged 1.7% to 7.9% Test Setting 13 juvenile detention centers (7.9%) and adult centers (6.8%) 11 community outreach setting (5.5%) Clinical setting (3.8%) including 14 male screening, 5 peds/adolescent, 4 HIV, 2 Emergency, 3 in other clinic setting 6 Military setting (4.5%) 12 School-based (4.6%) 2 mail-in (1.3%, 2.1%) Race/Ethnicity (26 studies) Blacks: 6.7% Asians: 2.2% Age group (12 studies) 20 to 24: 6.5% &lt;15: 2.3% Region (46 studies) South: 6.4% West: 3.8%</td>
<td>5: Study population: demographics not described, recruitment process not described Sampling: various locations and settings, no inclusion/exclusion criteria described for patient recruitment, groups not comparable Bias and confounding: Potential for publication bias was not mentioned in article, nor any need for adjustment in analysis. Analysis: Unclear in methodology for quality assessment and internal validity of study. Results: Only prevalence reported, no measures of statistical significance, only generalizable findings and inferences made.</td>
<td>Poor</td>
</tr>
</tbody>
</table>

CT=C. trachomatis, NAAT=nucleic acid amplification test
### Table 3. Summary of articles for adverse effects of screening (Key Question 3)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campbell R, et al, 2006</td>
<td>Question: Does home-based screening for Chlamydia have an adverse effect on</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>levels of anxiety, depression and self-esteem in those screened? If so, do</td>
<td>85,300 total 16 – 39 year old men and women registered at one of the 27 GPs in</td>
<td>842 people responded</td>
<td>In the first 4 GPs, cohort response was low over time, causing change in study design to cross-section of population.</td>
<td>After an interim analysis of first 4 practices, invitations for screening were narrowed to 16-25 year olds.</td>
<td>Survey: Hospital Anxiety and Depression Scale (HAD) for main outcome</td>
</tr>
<tr>
<td></td>
<td>anxiety scores return to pre-screening levels in those receiving negative</td>
<td>Bristol and Birmingham</td>
<td>• 218 before invitation</td>
<td>First 2 practices excluded for possibility of influences measurements surrounding publicity of study, ClasSS project.</td>
<td>First 2 practices excluded for possibility of influences measurements surrounding publicity of study, ClasSS project.</td>
<td>• 7 item subscale score 0-21</td>
</tr>
<tr>
<td></td>
<td>test results? Design: Cohort and cross-sectional study using questionnaires</td>
<td>Study packs were sent between Feb 2001 – Jul 2002</td>
<td>• 397 at invitation</td>
<td>Non-response was associated with practices with higher levels of “deprivation” OR = 0.88 (95% CI 0.80, 0.96; p=0.004), adjusted for age, sex, and ethnicity.</td>
<td>Non-response was associated with practices with higher levels of “deprivation” OR = 0.88 (95% CI 0.80, 0.96; p=0.004), adjusted for age, sex, and ethnicity.</td>
<td>• 0-7 normal</td>
</tr>
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<td>to assess psychosocial impacts of screening for Chlamydia</td>
<td>687 people from 13 practices invited in cohort sample</td>
<td>• 227 after (-) result</td>
<td>Adjusted for deprivation adjustment. no evidence of misrepresentation of ethnicity (OR=0.98, 95% CI 0.92-1.05; p=0.71)</td>
<td>Adjusted for deprivation adjustment. no evidence of misrepresentation of ethnicity (OR=0.98, 95% CI 0.92-1.05; p=0.71)</td>
<td>• 8-10 mild</td>
</tr>
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<td>1533 people from 12 practices invited in cross-sectional samples</td>
<td>• 547 before invitation</td>
<td>Self-selection potential high – more aware of risks, anxious about infection can be reflected in anxiety levels</td>
<td>Self-selection potential high – more aware of risks, anxious about infection can be reflected in anxiety levels</td>
<td>• 11 and &gt; in distress</td>
</tr>
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<td>• 418 at invitation</td>
<td>Under nationalized system, most individuals will have been registered with a GP – before randomization, can capture study population representative of source population.</td>
<td>Under nationalized system, most individuals will have been registered with a GP – before randomization, can capture study population representative of source population.</td>
<td>Survey conducted at three time points: baseline one-month before screening invitation, on receipt of screening with study packet, after receipt of negative test result</td>
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<td>• 227 after (-) result</td>
<td>Moderate external validity similar young population – can be comparable to US youth.</td>
<td>Moderate external validity similar young population – can be comparable to US youth.</td>
<td>Invitation letter from GP with study pack and instructions for home collection urine and/or vulval swab specimen, testing for Chlamydia.</td>
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<td>Negative results were informed by letter, positive results were sent appointment for follow-up with GP</td>
</tr>
</tbody>
</table>

GP=general practitioner, OR=odds ratio, CI=confidence interval

(cont.)
### Table 3. Summary of articles for adverse effects of screening (cont.)

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Measurement of exposure/outcome</th>
<th>Bias and Confounding</th>
<th>Analysis</th>
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<th>Limitations</th>
<th>Overall quality</th>
</tr>
</thead>
</table>
| Campbell R, et al, 2006 | Study pack complied with European regulations of mailing of clinical specimens | Acceptability and readability of study materials explored with 11 people chosen at random from those not selected for the prevalence study. | Planned to measure response in cohort of 1000 individuals, randomly sampled from all invited to be screened, stratified by age group, sex and practice. | Anxiety  
  Male (16-25): 6.52  
  Male (26-39): 6.27  
  Female (16-25): 8.14  
  Female (26-39): 8.28  
  Depression  
  Male (16-25): 3.01  
  Male (26-39): 4.12  
  Female (16-25): 3.63  
  Female (26-39): 4.42  
  Self-esteem  
  Male (16-25): 8.57  
  Male (26-39): 8.39  
  Female (16-25): 7.46  
  Female (26-39): 8.47  
  Overall anxiety over time:  
  Before invitation 0 (95% CI)  
  After invitation -0.66 (-1.23, -0.09)  
  Negative results -0.99 (-1.60, -0.38)  
  Overall p=0.0049, 0=0.012 interaction with sex  
  Overall depression over time:  
  Before invitation 0 (95% CI)  
  After invitation -0.47 (-1.09, 0.15)  
  Negative results -0.26 (-0.91, 0.39)  
  Overall p=0.25, 0=0.041 interaction with sex  
  Overall self-esteem over time:  
  Before invitation 0 (95% CI)  
  After invitation 0.12 (-0.26, 0.50)  
  Negative results -0.13 (-0.57, 0.31)  
  Overall p=0.26, 0=0.98 interaction with sex  
  | 2:  
  Study design:  
  Also, sampling of population changed from cohort to cross sectional. However, analysis showed comparable response rates and average main outcomes  
  | Good |

We used the first four practices to test methods to optimize the response rate: randomized different types of female swabs, questionnaires with or without sexual behavior questions, timing of letter from GP, and reminders, effect of a monetary incentive.

GP=general practitioner
Table 3. Summary of articles for adverse effects of screening (cont.)

<table>
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<tr>
<th>Study Reference</th>
<th>Study Design</th>
<th>Source Population</th>
<th>Study Population</th>
<th>Missing Data</th>
<th>Selection Bias</th>
<th>Intervention</th>
</tr>
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<tr>
<td>Kangas, I, et al., 2006</td>
<td>Question: Are there quantifiable concerns related to a test for Chlamydia in general practice?</td>
<td>Setting: Aarhus County, Denmark. Total Population 640,000; 274 general practices; 450 GPs</td>
<td>Recruitment: During visit to GP for Chlamydial testing, patients asked by GP for permission to mail further information and questionnaire for study participation. Criteria: Age 18 and above. Dates of recruitment: 18 March – 31 May 2002</td>
<td>25 general practices refused to participate, but there is no description of this population, however, unlikely to have large effect on study results</td>
<td>Does not clarify how patients were chosen for recruitment—age? Purpose of visit? Sexual history? Self-selection of participants – 159 participants refused study offer by GP. This can be because there is a high level of stigmatization or embarrassment, biasing towards the null. 18.8% of questionnaires were never mailed in. Unclear if patients already received positive of negative diagnosis. Either patients forgot, or may have been too embarrassed or felt stigmatized to continue with study.</td>
<td>Questionnaire based on identified topics of concern in separate studies of women: stigmatization, partner’s reaction, future reproductive health. Pre-stamped, pre-addressed mailed to participants within 1 week of testing. If no response after 2 weeks, reminder letter sent. For each question, asked if they “fully agreed,” “somehow agreed,” “somehow disagreed,” or “fully disagreed”</td>
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<tr>
<td></td>
<td>Design: Comparative cross-sectional study comparing psychosocial impacts of testing for Chlamydia between patients with positive and negative diagnosis</td>
<td>Source: All <em>C.trachomatis</em> samples in Aarhus Co. are analyzed in Aarhus Univ.Hospital. All potential participants identified through this sample submission. Appro. 90% of tests are in general practice Two weeks before study, GPs were sent letters to participate in recruitment process. 249 general practices accepted.</td>
<td>For each positive test result, three-four negative test results were matched by sex. 341 questionnaires mailed, with 81.2% response. N=277 • 54 (+) women • 122 (-) women • 28 (+) men • 73 (-) men Age 18-43, mean age=25, median age 24. Symptoms reported in 40% of men and 48% of women at time of testing.</td>
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GP=general practitioner
Table 3. Summary of articles for adverse effects of screening (cont.)

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| Kangas, I, et al., 2006 | For recruitment of general practices, no reminder was sent for practices that failed to respond | Probable high levels of selection bias. Patients are first selected GP who either request a test or the GP deems test necessary. Also, patients are approached by their GP to participate, and answer to appease GP and minimized negative effects of test. Also, unclear if all the questions were anonymous and any identifying information. Again, less likely to answer honestly. Unclear if patients were aware of diagnosis—can affect satisfaction with testing. | Questionnaire responses were dichotomized: an answer “fully agreed” or “somehow agreed” was considered “agreeing”; answers with “somehow disagreed” or “fully disagreed” as “disagreeing” Fisher’s exact two-tailed test and $\chi^2$ test with Yates correction. Significance was set to $p < 0.01$, adjusting for “multiple testing” of the questionnaire items. Mantel-Hansel analysis was used to adjust for age in subgroup analysis. Participants were dichotomized into two age groups, 18-25(n=183) and 26-43(n=94) Multiple subgroup analyses performed, but no indication in methodology for predetermined subgroup analysis SPSS 10.0 and STATA SE 8.0 were used. | Of 18 men who never considered STI infection and agreed to Chlamydia testing:  
- 88.9% satisfied with offer, (p=0.36)  
- 5.6% felt stigmatized, (p=0.31)  
- 5.6% had no emotional impact, (p=0.30)  
Of Chlamydia (+) men (n=28)  
- 50% considered test a private affair  
- 29% felt stigmatized  
- 46% think its embarrassing to talk about test  
In reaction to (+) test  
- 21% felt despair  
- 29% embarrassed  
- 32% no reaction  
Relation to partner  
- 75% was understanding  
- 43% were relieved  
- 11% ended  
Infertility  
- 68% Do not consider infertility a problem | 4: sampling method and potential for selection bias, validity and reliability of the measurement of exposure; attrition, loss to follow-up, identification and discussion of potential biases and confounding | Fair |

GP=general practitioner
Table 4. Summary of adverse effects of treatment (Key Question 4)

<table>
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<tr>
<th>Study Reference</th>
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<th>Study Selection</th>
<th>Population</th>
<th>Missing Data</th>
<th>Intervention</th>
<th>Measurement of exposure/outcome</th>
</tr>
</thead>
</table>
| Lau C, et al, 2002 | Question: Is there a difference between azithromycin or doxycycline in efficacy and safety in the treatment of *C. trachomatis* urethritis and cervicities? Design: Meta-analysis | Search: MEDLINE and Pre-Medline, HealthSTAR, Ovid Full Text, EBM reviews: Best Evidence, Cochrane Database of Systematic Reviews, and Database of Abstracts and Reviews of Effectiveness, and manual search. Time: 1975-August 2001 MeSH: Chlamydia trachomatis and doxycycline or C.trachomatis and Azithromycin | 12 trials • 5 masked • 7 open-label • 2 studies female only • 6 studies male only 1543 participants • 726 males • 817 females | Microbial cure was calculated using last available follow-up Intention-to-treat approach was used for attrition rates based on last available follow-up Patients with nongonococcal urethritis were used as proxies for those patients with CT infection when distinction of infection was not made Subjects lost to follow-up were excluded from the analysis | Various tests were used to diagnose disease. 9 studies used culture, 2 used enzyme immunoabsorbent assay, and 1 used DNA amplification tests. 7 studies were open-label and 5 were double-blinded Randomization scheme is not described for included studies. | Efficacy difference (ED) in cure rate between azithromycin and doxycycline was computed for each trial (treatment success/all subjects who began treatment) Treatment success = number of subjects assigned to a particular antibiotic group who complied with treatment regimen and cured at follow-up. There is no discussion on how information on adverse effects were tallied and scored. There is no mention of this was questionnaire, interview, and if this was made anonymous. Also, because of inconsistency of reporting, further analysis was not performed. | (cont.)
<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Lau CY, et al, 2002</td>
<td>A stratified meta-analysis was performed to assess possible bias in the results. Data were stratified by various subgroups: type of diagnostic assay (culture/nonculture), sex (male/female), attrition rate, follow-up time, publication date, study design (open/blind) and study sponsorship</td>
<td>Dichotomous outcomes (microbial cure versus no microbial cure) were pooled by calculating overall weighted average of the ED from each trial by assigning weights derived from the standard error of the ED. A similar approach was used to calculate the pooled risk difference (RD) of adverse events for the two antibiotics</td>
<td>Azithromycin group • microbial cure in 853 of 884 patients (96.5%) • adverse events were reported by 319 of 1274 (25.0%)</td>
<td>4: Study population: There was not much description of the study populations of the individual trials. Missing data: Excluding all data from those lost to follow-up cause an error that underestimates adverse effects, or decreases detection of adverse effects, although this may be minimal. Also, by using nongonococcal urethritis as proxies for CT infections, the investigators have increased likelihood of detecting adverse event from treatment regimens. Treatment is the same, and should have similar profile for adverse events</td>
<td>Fair</td>
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<td>Doxycycline group • microbial cure in 645 of 659 patients (97.9%). • adverse events were reported by 205 of 897 (22.9%)</td>
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<td>Pooled ED for microbial cure of azithromycin versus doxycycline is 0.008 (95% CI, -0.007–0.022) with ( Z = 1.05; P = 0.296 ). Test for homogeneity shows that results for individual trials are consistent with overall pooled ED ( \chi^2 = 10.48; df = 11; P = 0.488 ).</td>
<td>RD for an adverse event is 0.009 (95% CI, -0.019–0.037) with ( Z = 0.62; P = 0.533 ). Test for homogeneity shows that the results are consistent across trials ( \chi^2 = 6.63; df = 8; P = 0.577 ).</td>
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<td>Most frequently reported adverse events were gastrointestinal in nature (87.3%) including diarrhea, abdominal pain, nausea, vomiting, dyspepsia, constipation, and flatulence. Nongastrointestinal symptoms included fatigue, malaise, sweating, dizziness, headache, skin rash, drug eruption and other unspecified events</td>
<td>Exposure measurement: it is not clear what tools were used to diagnose Chlamydia in individual trials, and how study participants were randomized to study arms. The review is not clear in their methodology for appraising studies and discussing findings.</td>
<td></td>
</tr>
</tbody>
</table>

(continues)
REFERENCES


52. Horner P. Chlamydia (uncomplicated, genital). *Clin Evid (Online).* 2008.


